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Facio-Oculo-Acoustico-Renal (FOAR) Syndrome: Case Report and Review

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We report on an 11-year-old boy with distinct facial anomalies, iris coloboma, iris hypoplasia, cataract, high myopia, retinal detachment, moderate sensorineural hearing loss, and proteinuria. He appears to have the facio-oculo-acoustico-renal (FOAR) syndrome, a rare familial disorder reported only 4 times previously. In contrast to the other patients, he has normal intellect. Am. J. Med. Genet. 69:45–49, 1997.

KEY WORDS: coloboma; proteinuria; high myopia; hypertelorism; retinal detachment; sensorineural hearing loss; macrocephaly; deaf-blindness

INTRODUCTION

Facio-oculo-acoustico-renal (FOAR) syndrome is a rare familial disorder comprising prominent brow, flat nasal bridge, ocular hypertelorism, antimongoloid slant of the palpebral fissures, high myopia, iris hypoplasia or coloboma, cataracts, retinal detachment, sensorineural hearing loss, and proteinuria [Regenbogen and Coscas, 1985]. Recently we studied a patient with these findings. Like previously reported patients, he has a double sensory handicap with visual impairment and hearing loss; however, in contrast to the other patients, he had normal psychomotor development and milder hearing loss. We are reporting this patient to further define the phenotype of FOAR syndrome, one of the causes of deaf-blindness.

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CLINICAL REPORT

The patient was born at term to his 20-year-old G1 mother and 27-year-old father by an uncomplicated vaginal delivery following an unremarkable pregnancy. His mother did not identify any unusual exposures during the pregnancy. Birth weight was 3.4 kg (25th centile).

At age 2 years 11 months, he was referred to the University of Washington Eye Center for evaluation of reduced vision. Vision was central, steady and maintained; there was endpoint nystagmus on lateral gaze in each eye, more marked on the left. He had high myopia with a refractive error of about −20 diopters in each eye, a typical iris coloboma of the right eye, hypoplastic iris stroma inferior nasally in the left eye, and diffuse iris translumination bilaterally. His fundi were hypopigmented, and the retina and choroid had a stretched appearance; there was situs inversus of the disc and macular hypoplasia of both eyes. At 7 years, he developed total retinal detachment and hypotonia of the left eye from a flap tear which was repaired with a scleral buckling procedure. Resulting visual acuity OS was count-fingers. At 8 years he underwent vitrectomy with indirect laser and fluid/gas exchange for a recurrent total retina detachment, grade D-II proliferative retinopathy, and severe hypotonia. The left eye subsequently became phthisical, painless, and with no light perception. At age 10 years, a posterior subcapsular cataract developed OD, and at age 11 years visual acuity was 20/200 OD. Visual acuity at age 12 years following removal of the cataract OD was count-fingers at 1.5 m.

At 3 years, the patient was found to have a hearing loss which subsequently was characterized as bilateral, moderate, sensorineural and nonprogressive. Recurrent otitis media had required multiple tympanostomy tube placements until age 5 years. At age 10 years, he underwent tympanoplasty AD for persistent perforation attributed to his recurrent otitis media. His most recent hearing evaluation showed a 20 db loss at 250 Hz dropping to a 50 db loss at 1,000 Hz through the highest frequencies. Although he had not required amplification previously, at age 11 years he was fitted for binaural aids.

At age 11, the patient was found to have proteinuria along with 1+ occult blood, 0–1 renal tubular cells, and 1–5 hyaline casts. A 24 hour urine sample contained

3,172 mg of protein. Urine culture was negative. There was no aminoaciduria. Serum bicarbonate was 24, BUN 13 and creatinine 0.6 (all normal). Serologies for hepatitis B and C were negative. An antistreptolysin O (ASO) titer was elevated to 914 (normal 0 to 150). This was considered an unrelated finding since his other findings were not consistent with postinfectious glomerulonephritis. Levels of C3 and C4 were normal. Renal ultrasound findings were normal with no evidence of hydronephrosis, but the distal ureters were not well-visualized. A vesicoureterogram (VCUG) to evaluate possible vesicoureteral reflux was recommended, but not obtained.

The patient had no other major illnesses. Psychomotor development was normal. He sat by 6 months of age and walked at 12 months. His language development was normal. At age 11 years he was attending a regular 5th grade class, where he was an above average student. He also was receiving mobility training and was learning Braille.

Family history was unremarkable. The patient's mother had had a spontaneous abortion of triplets at 6 months of gestation. She had been adopted and there was no information on her birth family; nonetheless, consanguinity of the patient's parents was unlikely. The patient's father had 3 living sibs. The paternal grandparents were both alive and well at 60 years of age. The parents' eyes were examined and neither had findings similar to those of the propositus. No other relatives had known ocular abnormalities, hearing loss, renal disease, nor particularly distinctive facial appearance.

At 11 years 9 months, his height was 152 cm (95th centile), weight 53 kg (>97th centile), and occipitalfrontal circumference 59 cm (>98th centile). The patient (Fig. 1) had a prominent forehead, flat nasal bridge, and ocular hypertelorism with an inner canthal distance of 35 mm (98th centile) and an outer canthal distance of 11.5 cm (>98th centile). In the right eye there was a typical iris coloboma (Fig. 2). Evaluation of the right eye with an indirect ophthalmoscope demonstrated a hypopigmented fundus with no macular differentiation, many 500 μ diameter "punched-out" areas of retinochoroidal atrophy in the inferior nasal quadrant (Fig. 3A and B), and overlying vitreous debris. The disc was pink and had no cup. There was a scleral ridge on the temporal edge of the disc. The left eye was phthisical with corneal and lenticular opacities. His pinnae were normal as were the external auditory canals. The tympanic membranes were scarred. The palate was slightly narrow; all secondary teeth appeared normal. The chest was symmetric, and the heart findings were unremarkable. The liver and spleen were not palpably enlarged. The external genitalia were prepubertal and normal. The limbs were normal without hypermobility. The deep tendon reflexes were normal. The skin was unremarkable. The scalp hair was brown and of normal texture.

Fig. 1. Thirteen year-old boy with facial findings of FOAR syndrome including prominent brow, flat nasal bridge, ocular hypertelorism, and antimongoloid slant to the palpebral fissures. His left eye became phthisical following retinal detachment.

DISCUSSION

Our patient's distinct facial appearance, ophthalmologic, auditory, and renal findings are most consistent with the diagnosis of the FOAR syndrome. A Medline search of the literature since 1966 using the words "coloboma," "hearing loss," "hypertelorism," and "renal abnormalities" found only 4 reports of FOAR syndrome [Murdoch and Mengel, 1971; Fraser, 1976; Regenbogen and Coscas, 1985].

The findings in our patient (patient 5) and those previously reported are summarized in Table I. The first two (patients 1 and 2) were a brother and sister who were independently reported 3 times [Murdoch and Mengel, 1971; Holmes and Schepens, 1972; Ozer, 1974]. Less is known about patients 3 [Fraser, 1976] and 4 [Regenbogen and Coscas, 1985] because limited information was presented.

All previously reported patients had distinct facial changes including a flat nasal bridge, ocular hypertelorism, and in 3 of the 4 cases a prominent brow or antimongoloid slant of the palpebral fissures; they also had moderate to severe sensorineural hearing loss, proteinuria, severe myopia, and poor vision. Three of the 4 previously reported patients had iris coloboma and/or iris transillumination defects. Two of these 3 (patients 1 and 4) had retinal detachment with unsuccessful surgical repair which is remarkably similar to the findings in our patient. Our patient had reduced vision in his better eye presumably from a combination of his high myopia, chorioretinal atrophy, and poorly differentiated macula.

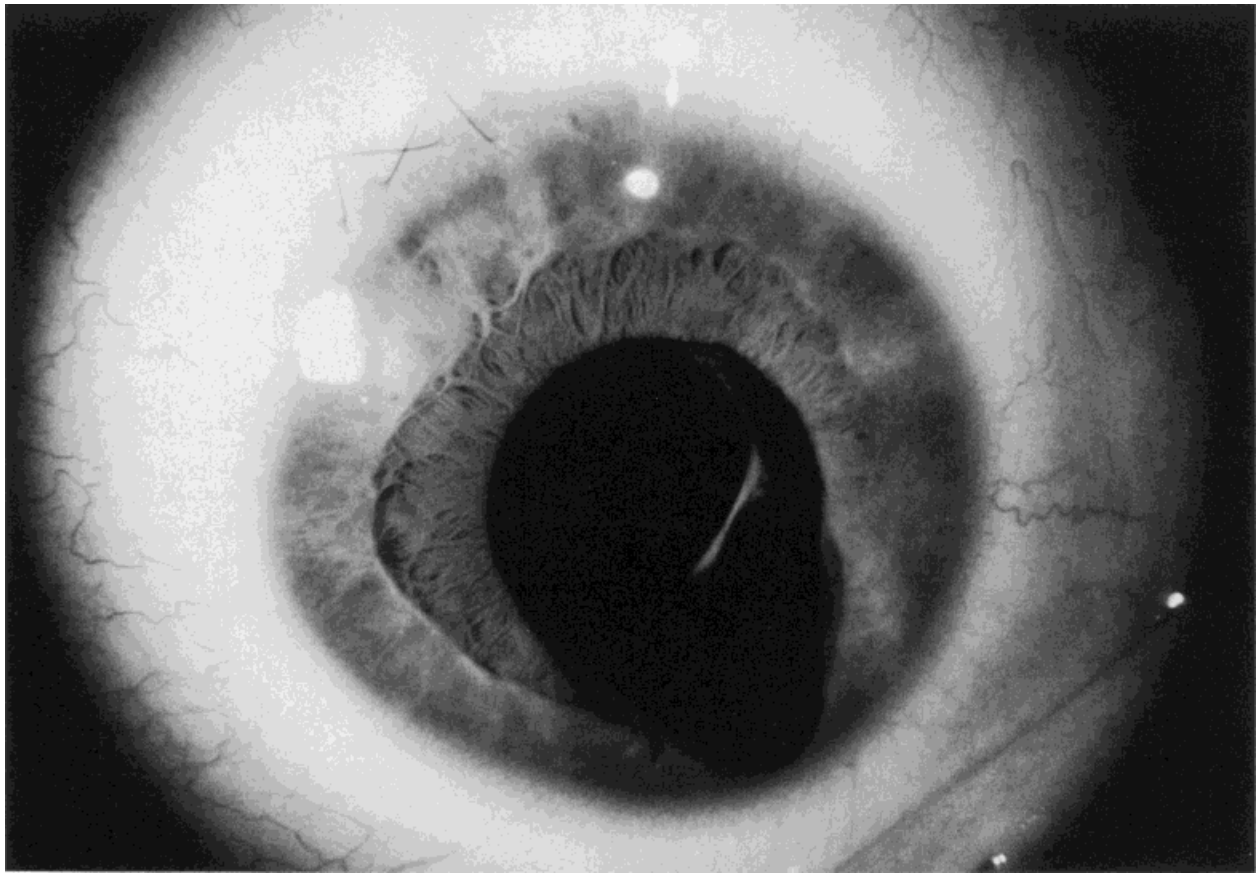

Fig. 2. Typical iris coloboma OD. The photograph was taken following cataract extraction and lense implantation (sutures are residua of that operation).

The ocular complications in FOAR syndrome are more severe than those usually anticipated in patients with coloboma. Retinal detachment, occurring at the interface of the normal retina and coloboma, is a recognized complication of choroidal coloboma [Schubert, 1995]. However, retinal detachment is not expected when the colobomatous malformations affect only the iris as in FOAR syndrome. Thus, the predisposition to retinal detachment in FOAR syndrome may result from the extremely high myopia with choroidal atropy and staphyloma. In addition, the other reported ocular complications in FOAR syndrome such as early-onset cataracts and anterior chamber anomalies predisposing to glaucoma, are not characteristic of typical coloboma. Thus, it appears that there is panocular pathology in this syndrome. These extensive ocular abnormalities require close ophthalmologic follow-up to facilitate diagnosis and management of treatable complications. Children with FOAR syndrome, who are at high risk for visual impairment, need prompt referral to support services for the visually and hearing impaired.

The normal psychomotor development of our patient, and his success in school are in contrast to other reported patients with FOAR. Patient 1 was hyperactive, and considered moderately mentally retarded. His sister, patient 2, had normal intelligence, but had the least severe eye findings of all reported cases. No developmental information was provided on patient 3. Patient 4 had "subnormal psychomotor development" and was considered "mentally retarded to a moderate degree."

Although our patient and 2 of the 4 previously described patients with FOAR syndrome have had no other affected relatives, two of the reported patients (1 and 2) were affected sibs which suggests autosomal recessive inheritance, but is also consistent with autosomal dominant inheritance.

The skeletal, ocular, otic, and renal abnormalities found in all 5 patients suggests that a mutation in a gene required for the development of all of these systems could result in FOAR syndrome. Recently, a PAX2 gene mutation was identified in a family with optic nerve coloboma, renal anomalies, and vesicoureteral reflux which appears to be inherited in an autosomal dominant fashion [Sanyanusin et al., 1995]. We suggest that a different mutation in PAX2 may be responsible for FOAR syndrome.

ACKNOWLEDGMENTS

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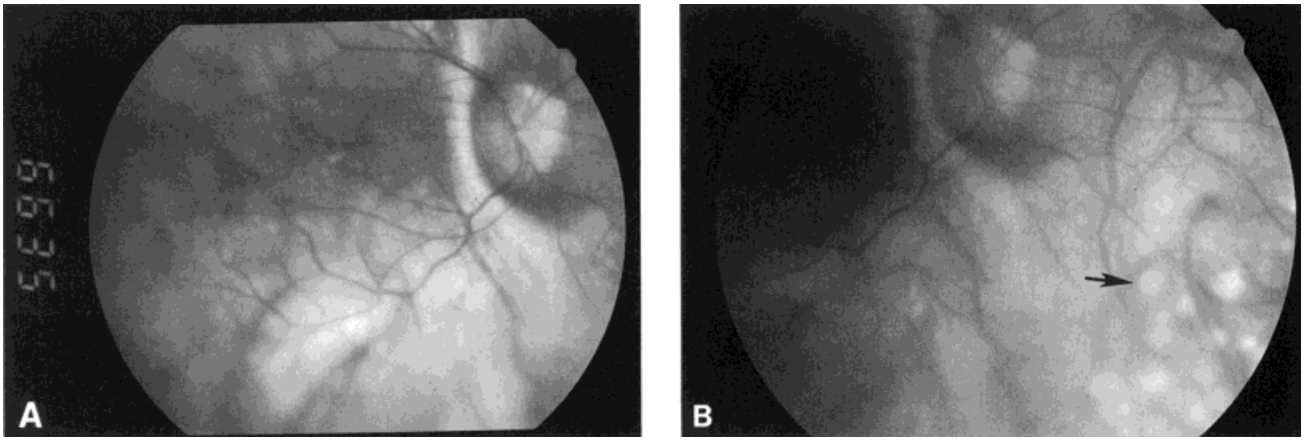

Fig. 3. **A**: Fundus (OD) at age 13 is hypopigmented (especially inferior temporally) with no macular differentiation and a scleral ridge temporally on the disc. **B**: Note the 500 μ diameter "punched-out" areas of retinochoroidal atrophy (arrow) in the inferior nasal quadrant.

TABLE I. Phenotypic Manifestations Seen in Patients With FOAR Syndrome

	Patient				
	1	2	3	4	5
Sex	M	F	M	M	M
Ocular					
Iris coloboma	+	−			+
Iris hypoplasia/heterochromia	+	+		+	+
Abnormal anterior chamber	+	+		+	−
Cataract	+	−			+
Vitreous organization	+	−			
Staphyloma/choroidal atrophy	+	+			+
Refractive error	−24D[a]	−10D	HM	−12D	−20D
Abnormal disc		+			Pale
Retinal detachment	+	−		+	+
Poor vision	+	+	+	+	+
Acoustic					
Sensorineural hearing loss	Severe	Severe	+	Severe	Mod
Renal					
Proteinuria	+	+	+	+	+
Hematuria					+
Aminoaciduria	+	+			
Structural abnormalities	+	−			−
Renal failure	+				−
Characteristic facial findings					
Prominent brow	+		+	+	+
Flat nasal bridge	+	+	+	+	+
Ocular hypertelorism	+	+	+	+	+
Antimongoloid slant to PF	+	+	+	−	+
Other					
Macrocephaly	+	+		+	+
Delayed closure ant. fontanelle	+	+			
Mental ability	MR	Normal		Mod MR	Normal
Hyperactivity	+				−
Language development	No speech	No speech			Normal
Motor development	Delayed	Delayed			Normal
Hernia	Ing/umb	−	Umb	−	−
Karyotype	Normal	Normal			

[a] D, diopters; Mod, moderate; MR, mental retardation; ing, inguinal; umb, umbilical; HM, high myopia; PF, palpebral fissures.

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